broths of *A. terreus* cultures expressing lovE variant proteins 1-10 in MF117.

Figure 7B is a graphic depiction of lovastatin culture concentration, as measured by HPLC analysis, from broths of *A. terreus* cultures expressing lovE variant proteins 2, 6, 30, 32, 36, 37, 39, and 41 in MF117.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

The patents and publications cited herein reflect the level of knowledge in the art and are hereby incorporated by reference in their entirety. Any conflict between any teaching of such references and this specification shall be resolved in favor of the latter.

The invention utilizes techniques and methods common to the fields of molecular biology, genetics and microbiology. Useful laboratory references for these types of methodologies are readily available to those skilled in the art. See, for example, Molecular Cloning, A Laboratory Manual, 3rd edition, edited by Sambrook, J., MacCallum, P., and Russell, D.W. (2001), Cold Spring Harbor Laboratory Press (ISBN: 0-879-69576-5); Current Protocols In Molecular Biology, edited by Ausubel, F.M., Brent, R., Kingston, R.E., Moore, D.D., Seidman, J.G., Struhl, K. (1993), John Wiley and Sons, Inc. (ISBN: 0-471-30661-4); PCR Applications: Protocols for Functional Genomics, edited by Innis, M.A., Gelfand, D.H., Sninsky, J.J. (1999), Cold Spring Harbor Press (ISBN: 0-123-72186-5); and Methods In Yeast Genetics, 2000 Edition: A Cold Spring Habor Laboratory Course Manual, by Burke, D., Dawson, D. and Stearns, T., Cold Spring Harbor Press (ISBN: 0-879-69588-9).

In certain embodiments of the aspects of the invention, the invention relates to the biosynthesis and improved production of secondary metabolites. The invention provides variant regulator proteins useful for the production of secondary metabolites, nucleic acid molecules encoding variant regulator proteins, and methods for their production.

In a first aspect, the invention provides a variant regulator protein of secondary metabolite production with increased activity relative to a cognate, wild-type regulator protein. Particularly preferred are variant regulator proteins of fungal secondary metabolites.

As used herein, the terms "fungal" and "fungus" refer generally to eukaryotic, heterotrophic organisms with an

absorptive mode of nutrition. Fungi typically contain chitin in their cell walls and exhibit mycelial or yeast-like growth habits (More Gene Manipulations in Fungi, edited by J.W. Bennet and L.L. Lasure, Academic Press Inc. (1991), ISBN 0120886421). More specifically, the terms refer to secondary metabolite producing organisms including, without limitation, *Aspergillus sp., Penicillium sp., Acremonium chrysogenum, Yarrowia lipolytica, Nodulisporium sp., Fusarium sp., Monascus sp., Claviceps sp., Trichoderma sp., Tolypocladium sp., Tricotheicium sp., Fusidium sp., Emericellopsis sp., Cephalosporium sp., Cochliobolus sp., Helminthosporium sp., Agaricus brunescens, Ustilago maydis, Neurospora sp., Pestalotiopsis sp.* and *Phaffia rhodozyma* (*See*, Fungal Physiology, Chapter 9 (Secondary(Special) Metabolism), Griffin, D. H., John Wiley & Sons, Inc.; ISBN: 0471166154).

The term "variant regulator protein" is used herein to refer to any regulatory protein having at least one change or difference in the amino acid sequence of the protein when compared to its cognate, wild-type regulatory protein sequence. The term does not include naturally occurring allelic variations of the cognate, wild-type regulatory protein.

The term "regulator protein" is meant to refer to a protein having a positive or negative function that modifies the production of a secondary metabolite. The function of the protein may be at the level of transcription, e.g., repression or activation, protein synthesis, or transport. The regulator may alter the level of transcription, RNA stability, translation, post-translational modification, or cellular localization of proteins involved in secondary metabolite synthesis and/or transport. The regulator may also have effects on precursor metabolite pools, flux through specific pathways and metabolite resistance.

By way of non-limiting example, certain embodiments of the aspects of the invention relate to a regulator protein that is a protein that contributes and/or promotes